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A mathematical model of the bovine oestrous cycle: Simulating outcomes of dietary and pharmacological interventions

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HIGHLIGHTS

- We use differential equations to predict hormone changes in the bovine oestrous cycle.
- The model simulates control and feedback mechanisms between brain and ovaries.
- Predictions agree with known biology and experimental observations.
- Effects of animal, nutrition and hormone treatment on ovulation are predicted well.

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ABSTRACT

A mathematical model was constructed to simulate the bovine oestrous cycle by using nonlinear differential equations to describe the biological mechanisms which regulate the cycle. The model predicts circulating concentrations of gonadotrophin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, oestradiol, inhibin and progesterone. These hormones collectively provide control and feedback mechanisms between the hypothalamus, pituitary gland and ovaries, which regulate ovarian follicular dynamics, corpus luteum function and ovulation. When follicular growth parameters are altered, the model predicts that cows will exhibit either two or three follicular waves per cycle, as seen in practice. Changes in other parameters allow the model to simulate: effects of nutrition on follicle recruitment and size of the ovulatory follicle; effects of negative energy balance on postpartum anoestrus; and effects of pharmacological intervention on hormone profiles and timing of ovulation. It is concluded that this model provides a sound basis for exploring factors that influence the bovine oestrous cycle in order to test hypotheses about nutritional and hormonal influences which, with further validation, should help to design dietary or pharmacological strategies for improving reproductive performance in cattle.

1. Introduction

The bovine oestrous cycle is a repeating pattern of hormonal and physiological changes regulated by control mechanisms that orchestrate endocrine signals between the hypothalamus, pituitary gland and ovaries. The length of a cycle is defined as the time between successive ovulations which averages 21 days in normal cycles, but can range from 18 to 24 days (Forde et al., 2011). Cattle are monovulatory (they usually produce one oocyte per cycle) and modern breeds do not exhibit strong seasonal or lactational anoestrus (cessation of cycles, as seen in sheep and pigs for example). In post-pubertal cattle, therefore, cyclicity normally continues until interrupted by pregnancy and resumes between 20 and 30 days postpartum.

In dairy cattle, genetic selection has resulted in significant increases in milk yield per cow over the past 30 years, but this has been accompanied by a decline in reproductive performance (Royal et al., 2000). Poor reproductive performance not only causes financial losses for producers, but also increases the environmental impact of dairy farming (Garnsworthy, 2004). The study of Royal et al. (2000) revealed that between 1975–1982 and 1995–1998 the percentage of cows that became pregnant to first postpartum insemination had declined from 55.6% to 39.7%, which was attributed to an increase in the proportion of cows exhibiting atypical ovarian hormone patterns from 32% to 44%. Atypical ovarian hormone patterns, such as extended anoestrus or prolonged high progesterone concentrations,

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often require pharmacological intervention before normal cycles can be resumed. Recent studies have shown, however, that manipulation of the diet can reduce the incidence of atypical cycles (Gong et al., 2002; Garnsworthy et al., 2008a). These studies found that atypical cycles are associated with low circulating concentrations of insulin, but the relationship involves multiple interactions among nutrition, genetics and physiological state (Garnsworthy et al., 2008a). The complexity of these interactions suggests that a systems biology approach can be adopted to seek better understanding of the mechanisms linking nutrition to fertility.

Nutrition has major effects on bovine fertility, although the links are complex with many inter-related factors involved (Garnsworthy et al., 2008a). At the simplest level, postpartum energy balance (the difference between energy consumed and energy utilised for maintenance and milk synthesis) affects the number of follicles, their rate of growth and development, and size of the ovulatory follicle (Lucy et al., 1991; Boland et al., 2001; Butler, 2003). Dairy cows typically undergo a period of negative energy balance in early lactation and the greater the degree and duration of negative energy balance, the longer the period between parturition and first ovulation (Butler, 2003). This effect is largely independent of circulating gonadotrophin concentrations (Boland et al., 2001; Webb et al., 2004), although negative energy balance does attenuate LH pulse frequency (Butler, 2003) and higher-yielding cows have greater rates of steroid clearance due to increased blood flow through the liver resulting from increased dry matter intake (Wiltbank et al., 2006). The effect is not due to energy demands of growing follicles, which are negligible compared to requirements of the cow for maintenance and milk production. It appears, therefore, that nutritional effects on follicular recruitment and growth are mediated mainly by metabolic signals to the ovary that vary with metabolic status (Lucy, 2003; Webb et al., 2004). The primary signal of metabolic status is insulin and research demonstrated that diets designed to increase insulin status of dairy cows in early lactation can increase the proportion of cows ovulating before 50 days postpartum, even when cows are in negative energy balance (Gong et al., 2002). Insulin is related positively to dietary starch (Garnsworthy et al., 2008b) and protein (Garnsworthy et al., 2008a) contents, and negatively to dietary fat content (Garnsworthy et al., 2008c), and higher plasma insulin concentrations stimulate follicle recruitment (Garnsworthy et al., 2008b). Excessive insulin can reduce the quality of oocytes, however, and significant improvements in pregnancy rate were observed by feeding a diet to stimulate insulin in the early postpartum period and then switching to a diet that reduced insulin during the mating period (Garnsworthy et al., 2009). Optimising fertility by varying the diet is a key tool available to farmers to improve reproductive performance, thereby increasing the sustainability of dairy farming(Garnsworthy, 2004; Maas et al., 2009).

The bovine oestrous cycle displays rich dynamical behaviour in terms of regular follicular waves and resulting ovulations. The cycle has been studied in detail (Evans et al., 1994; Armstrong and Webb, 1997; Ginther et al., 1998; Campbell et al., 1999; Ginther et al., 2002; Adams et al., 2008; Garnsworthy et al., 2008a; Aerts and Bols, 2010) and mathematics can play a key role in describing and understanding the underlying control mechanisms. Mathematical models offer opportunities to vary model parameters in ways that would be impossible in vivo, one at a time for example; they can also suggest mechanistic interactions that might not be apparent from studying animal inputs and responses. Furthermore, models enable simulation of a wide range of physiological and nutritional scenarios which would require prohibitive resources to test by animal experimentation; predictions can then be used to design experiments that are most likely to yield significant results.

The paper of Blanc et al. (2001) reviewed mathematical models of reproduction in farm animals and concluded that mechanistic influences of nutrition on reproduction were largely unexplored. Many models focus on specific aspects of the reproductive system and are not, therefore, at a level where nutritional effects can be correctly included in the model. A review by Vetharaniam et al. (2010) concurred with this view and added that differences between models can reflect differences in level of understanding of the biological pathways involved. Thus, contrasting approaches are seen in models of GnRH secretions, where competing mechanisms have been postulated, whereas models of follicular growth tend to be less hypothetical due to general agreement about underlying mechanisms.

A model by Lacker (1981) and Lacker et al. (1987) was based on the assumption that developing follicles communicate through circulating hormones to determine follicle growth. All follicles inherit the same developmental plan, but interactions among follicles result in differentiation into ovulatory and atretic follicles. Further development of Lacker's model by Chavez-Ross et al. (1997) treated follicles as having different sensitivities to gonadotrophins. A model developed by Soboleva et al. (2000) and Smith et al. (2005) considered oestradiol produced by individual follicles as being governed by circulating luteinizing hormone (LH) concentration and the sensitivity of the hypothalamus to oestradiol. These two models of the oestrous cycle, Soboleva et al. (2000) and Lacker (1981), predict oestradiol concentrations, but are not sufficiently detailed to incorporate nutritional effects. In the model of Smith et al. (2005), however, a parameter that controls the sensitivity of the ovarian response to LH has been linked with postpartum levels of insulin (Pleasants et al., 2005), which can be altered by nutrition Garnsworthy et al. (2008a).

Most of the models reviewed in Blanc et al. (2001) do not explicitly include biological feedback mechanisms between the hypothalamus, pituitary gland and ovaries, but we believe this is crucial in obtaining a robust mathematical model of the bovine oestrous cycle. The review by Vetharaniam et al. (2010) suggests that complex details of underlying mechanisms are not necessarily beneficial because an increased number of parameters can reduce the stability of predictions, whereas more empirical models can sacrifice these details to optimise practicality and utility. In this paper, we build upon work by Selgrade and Schlosser (1999), Schlosser and Selgrade (2000) and Clarke et al. (2003), who modelled the human menstrual cycle with biological feedback mechanisms included at the scale which we wish to consider. Significant changes to their models are made in order to account for physiological differences between regulatory mechanisms in the human menstrual cycle and the bovine oestrous cycle. A similar approach was taken in a paper published after our study was completed (Boer et al., 2011), in which a mathematical model of the bovine oestrous cycle was presented that simulates follicle development and accompanying fluctuations in hormone concentrations. Although Boer et al. (2011) speculated about the application of their model to study effects of external influences on the cycle, our aim from the outset was to produce a framework for modelling the bovine oestrous cycle which links nutrition, metabolism and reproduction.

The objective of the current study was to explore further how the bovine oestrous cycle can be modelled, allowing us to investigate mathematically the effects of diet and pharmacological interventions on the dynamics of the system.

2. Modelling the bovine oestrous cycle

2.1. Preliminaries

As mentioned previously, the bovine oestrous cycle is regulated by control mechanisms involving the hypothalamus, pituitary gland and ovaries. We aim to capture these natural control mechanisms and later we show that follicular wave patterns and

hormone levels predicted by our model are consistent with experimental data. The model relies on differential equations to describe rates of change in hormone concentrations, growth of follicles and the corpus luteum.

The biological feedback mechanisms which control hormone concentrations are modelled using Hill functions (Murray, 2005), which have a value between 0 and 1. For negative feedback the generic Hill function is defined as

$$H_-(x;n,T)=\frac{1}{1+(x/T)^n}$$

and for positive feedback the generic Hill function is defined as

$$H_+(x;n,T)=\frac{(x/T)^n}{1+(x/T)^n}$$

In each function, x is the concentration of the hormone providing feedback, T is the threshold concentration at which feedback is switched on or off, and n is the sharpness or suddenness of the switch with larger values of n giving a sharper on/off switching effect.

2.2. Hypothalamus–pituitary axis

The hypothalamus–pituitary axis plays a crucial role in regulating the bovine oestrous cycle through release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, and follicle stimulating hormone (FSH) and LH from the pituitary gland. These hormones affect growth of ovarian follicles and the corpus luteum, and timing of ovulation. Many processes occur within the hypothalamus–pituitary axis and now we describe how biological feedback mechanisms control release of GnRH, FSH, and LH.

Rate of change in bloodstream concentration of LH, dLH/dt, is a function of the amount of LH *released* from the pituitary gland into the bloodstream and the amount *cleared* from the bloodstream, either by the liver or through normal degradation of the hormone. Release of LH from the pituitary gland is controlled by episodic release of GnRH from the hypothalamus (Baird et al., 1981; Vizcarra et al., 1997; Pawson and McNeilly, 2005) and clearance of LH from the bloodstream is assumed proportional to the concentration of LH in the bloodstream. To model the positive effect of GnRH on release of LH we use a positive Hill function H_+. Thus the rate of change in concentration of LH is given by the following equation:

$$\frac{dLH}{dt}=k_{LH}H_+(GnRH;n_{LH,GnRH},T_{LH,GnRH})-\alpha_{LH}LH. \quad (1)$$

Here, the rate of clearance of LH from the bloodstream is parameterised by α_{LH} and for the rest of the paper we denote clearance rate of a hormone by α_i where i is replaced with the hormone name, e.g. FSH, GnRH etc. The term $k_{LH}H_+(GnRH;n_{GnRH},T_{GnRH,LH})$ denotes release of LH (as a function of $GnRH$) and since $0\le H_+(GnRH;n_{GnRH},T_{GnRH,LH})<1$ then parameter k_{LH} mathematically represents the maximum release rate of LH from the pituitary gland into the bloodstream.

Release of GnRH from the hypothalamus occurs in a series of pulses, with its release being a function of the ovarian hormones progesterone and oestradiol (Cruz et al., 1997; Padula and Macmillan, 2005). Frequency of GnRH pulses is higher during the follicular phase than during the luteal phase of the oestrous cycle. However, modelling individual pulses of GnRH adds mathematical complexity to the model which we believe is unnecessary in the current context. Sampling of pituitary portal blood at 30-s intervals revealed that the contour of most GnRH pulses approximates a square wave with a 50-fold increase in GnRH concentration within 1 min of pulse onset, a plateau lasting 1.5 to 8.5 min, followed by a rapid decline to baseline values within 3 min (Moenter et al., 1992). To model this would entail working at the 1-min scale and such resolution would be lost over the period of a 21-day cycle. Functionally, pulse frequency effectively determines pituitary portal concentration of GnRH; mathematically, we are interested in the strength of the GnRH signal that controls LH release from the pituitary and modelling GnRH release as a continuous process appears to give good results.

We assume that release of GnRH is a function of concentrations of progesterone and oestradiol in the bloodstream (Bergfeld et al., 1996) with progesterone having a negative feedback effect and oestradiol having a positive effect. Clearance rate of GnRH is assumed proportional to bloodstream concentration of GnRH. The model also includes the biological phenomenon whereby a surge of GnRH is released when oestradiol reaches a critical level, which occurs when the dominant follicle reaches a threshold size. To model effects of these negative and positive feedback mechanisms on GnRH we use the following equation:

$$\frac{dGnRH}{dt}=k_{GnRH}H_-(P_4(t);n_{GnRH,P_4},T_{GnRH,P_4})H_+(E_2(t);n_{GnRH,E_2},T_{GnRH,E_2})-\alpha_{GnRH}GnRH. \quad (2)$$

We note that multiplying the two Hill functions, H_- and H_+, in the above equation has the effect that a surge in GnRH release in response to oestradiol (E_2) can only occur if progesterone (P_4) levels are sufficiently low.

FSH is released from the pituitary gland and we model its rate of release as a function of concentrations of the three hormones inhibin, oestradiol and GnRH. It is known that inhibin and oestradiol both suppress release of FSH whereas GnRH promotes it (Ginther et al., 2001; Beg et al., 2002). Therefore, denoting bloodstream concentrations of inhibin as Ih and oestradiol as E_2, the equation used to model FSH concentration is

$$\frac{dFSH}{dt}=k_{FSH}H_-(Ih(t);n_{FSH,Ih},T_{FSH,Ih})H_-(E_2(t);n_{FSH,E_2},T_{FSH,E_2})+k_{FSH,GnRH}H_+(GnRH;n_{FSH,GnRH},T_{FSH,GnRH})-\alpha_{FSH}FSH. \quad (3)$$

Here we have multiplied together the two negative Hill functions for inhibin and oestradiol because these act together to suppress release of FSH, whereas a separate (independent) positive Hill function is used to model the positive effect of GnRH on FSH release.

A list of the parameters used so far is given in Table 1, which includes a biological description of each parameter. Values for these parameters were derived through testing the model against our biological understanding and observations of the bovine oestrous cycle, and clearance rates were estimated from the half-life of each hormone. For example, the average half-life of LH peaks in Rahe et al. (1980) was 116.6 min, so the clearance rate of LH is estimated as $[\ln(2)/(116.6\times1440)]=8.56$ ng ml^{-1} d^{-1}. There was no formal parameter estimation, but initial estimates derived from the literature were tuned manually until model outputs agreed with experimental observations. The main sources of comparison data for testing parameters in Tables 1 and 2 were Rahe et al. (1980); Webb et al. (1980); Peters and Lamming (1984); Vizcarra et al. (1997); Ginther et al. (2002); Gong et al. (2002); Padula and Macmillan (2005); Pawson and McNeilly (2005); Medan et al. (2006); Wiltbank et al. (2006).

2.3. Ovarian model

We now turn our attention to modelling changes within the ovaries that occur during the oestrous cycle. In addition to changes in concentrations of hormones, we also need to model the dynamics of recruitment, selection and dominance of follicles, and growth and luteolysis of the corpus luteum. To do this we again make use of the work on the human menstrual cycle by

Table 1
Parameters used in Eqs. (1)–(3) to model the hypothalamus–pituitary axis control of bloodstream concentrations of GnRH, FSH and LH.

Parameter	Value	Units	Biological description
k_{LH}	75	ng ml^{-1} d^{-1}	Release rate of *LH*
$n_{LH,GnRH}$	10		Exponent for positive effect of *GnRH* on *LH*
$T_{LH,GnRH}$	5	pg ml^{-1}	Threshold value, positive effect of *GnRH* on *LH*
α_{LH}	8.56	d^{-1}	Natural clearance rate of *LH*
k_{GnRH}	12.84	pg ml^{-1} d^{-1}	Release rate of *GnRH*
n_{GnrH,P_4}	5		Exponent for negative feedback of P_4 on *GnRH*
T_{GnRH,P_4}	5	ng ml^{-1}	Threshold value, negative feedback of P_4 on *GnRH*
n_{GnrH,E_2}	10		Exponent for positive feedback of E_2 on *GnRH*
T_{GnRH,E_2}	3	pg ml^{-1}	Threshold value, positive feedback of E_2 on *GnRH*
α_{GnRH}	2.14	d^{-1}	Natural clearance rate of *GnRH*
k_{FSH}	12.84	ng ml^{-1} d^{-1}	Release rate of *FSH*
$n_{FSH,Ih}$	2		Exponent for negative feedback of *Ih* on *FSH*
$T_{FSH,Ih}$	2	ng ml^{-1}	Threshold value, negative feedback of *Ih* on *FSH*
n_{FSH,E_2}	10		Exponent for negative feedback of E_2 on *FSH*
T_{FSH,E_2}	1.9	ng ml^{-1}	Threshold value, negative feedback of E_2 on *FSH*
$k_{FSH,GnRH}$	1.07	ng ml^{-1} d^{-1}	Release rate of *FSH* due to *GnRH*
$n_{FSH,GnRH}$	1		Exponent for positive effect of *GnRH* on *FSH*
$T_{FSH,GnRH}$	1	ng ml^{-1}	Threshold value, positive effect of *GnRH* on *FSH*
α_{FSH}	2.14	d^{-1}	Natural clearance rate of *FSH*

Table 2
Parameters controlling follicular and corpus luteum growth and the production of oestradiol, inhibin and progesterone by the ovaries.

Parameter	Value	Units	Biological description
a	0.0107	l d^{-1}	Sensitivity of pre-antral follicles to *FSH*
c_1	0.321	ml ng^{-1}d^{-1}	Growth rate of follicles due to *FSH*
c_2	0.749	d^{-1}	Rate of disappearance of recruited follicles
c_3	0.749	d^{-1}	Rate of disappearance of selected follicles
c_4	0.749	d^{-1}	Rate of atresia of dominant follicle
p_1	0.214	d^{-1}	Growth parameter for selected follicles
p_2	0.214	d^{-1}	Growth parameter for dominant follicle
e_0	0.0107	pg ml^{-1}	Basal concentration of oestradiol
e_1	2.14	kl^{-1}	Production of oestradiol by selected follicles
e_2	10.7	kl^{-1}	Production of oestradiol by dominant follicle
α_{E_2}	1.07	d^{-1}	Clearance rate of oestradiol
h_0	0.107	ng ml^{-1}	Basal concentration of inhibin
h_1	3.21	kl^{-1}	Production of inhibin by selected follicles
h_2	3.21	kl^{-1}	Production of inhibin by dominant follicle
α_{Ih}	1.07	d^{-1}	Clearance rate of inhibin
r_{growth}	3.21	d^{-1}	Growth rate of corpus luteum
r_{decay}	1.353	d^{-1}	Decay rate of corpus luteum
CL_{max}	10	mg	Maximum functional mass of corpus luteum
c_{P_4}	1.07	µl d^{-1}	Rate of production of progesterone
α_{P_4}	1.07	d^{-1}	Clearance rate of progesterone
$Total_{P_4}$	121.5	ng ml^{-1} d	Total amount of progesterone exposure to cause prostaglandin-F2α release
$T_{ov,LH}$	5	ng ml^{-1}	Threshold value for LH surge before ovulation

Selgrade and Schlosser (1999), Schlosser and Selgrade (2000) and Clarke et al. (2003). Our aim in modelling the ovaries is to reproduce the wave-like pattern of follicle growth. In addition, we wanted to model oestrous cycles with either two or three follicular waves per cycle, thereby simulating differences observed between individual cows (Ginther et al., 2001; Kulick et al., 2001; Ginther et al., 2002).

In this paper, we represent growth of follicles as an increase in their functional mass, i.e. their ability to produce hormones. This has a direct relationship with diameter of follicles, which is a measurement commonly reported in experiments. In Aerts and Bols (2010) growth of a follicle is divided into four stages: primordial follicle (ovarian reserve), recruitment, selection and dominance. A detailed description of each stage is given in Aerts and Bols (2010), but essentially during the recruitment stage we assume follicles are less than 6 mm in diameter and that they are responsive to FSH (Medan et al., 2006). Not only does FSH affect the number of follicles that enter the recruitment stage, but also follicles are dependent on FSH for continued growth in this stage

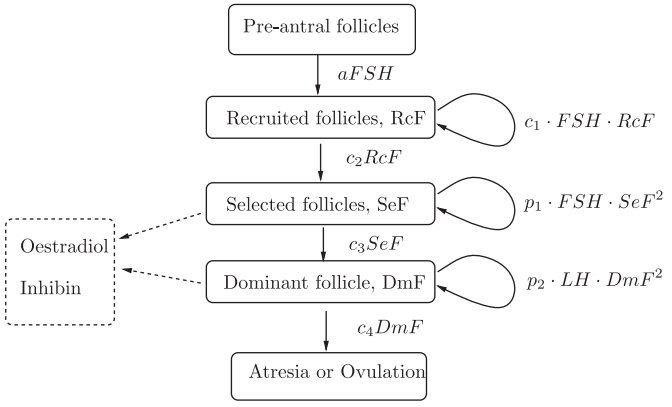

Fig. 1. The stages of growth of a follicle are 'recruited', 'selected' and 'dominant'. Functional mass of follicles in each stage is denoted by *RcF*, *SeF* and *DmF*. Arrows show transfer of follicles between stages, or net growth of functional mass within a stage (i.e. the sum of increase in functional mass due to follicle growth and decrease due to atresia).

and FSH affects their rate of growth (Webb et al., 2004). Follicles in the selected stage have diameters between 6 mm and 8 mm and still respond to FSH, but have not yet developed LH receptors. In the dominant stage, when a single follicle becomes dominant and all other follicles undergo regression (atresia), control of follicle growth switches from FSH to LH (Webb et al., 2004). These stages of growth, and their hormonal regulation, are shown in Fig. 1.

Rather than modelling evolution of masses for individual follicles, we instead model the *total* functional follicular mass in each stage. The rate of growth of follicles in the recruited stage is assumed to be a function of three different components: (i) the number of follicles recruited from the ovarian reserve of primordial follicles, (ii) the actual growth rate of follicles within the recruited stage and (iii) the number of follicles leaving the recruited stage, either by undergoing atresia or transferring to the selected stage. To model *RcF*, we use the following equation:

$$\frac{dRcF}{dt} = aFSH + (c_1 FSH - c_2)RcF. \tag{4}$$

The term $aFSH$ denotes the transfer of follicles from the ovarian reserve into the recruited stage; this is a function of FSH concentration in the bloodstream. Growth of follicles within the recruited stage is represented by the term $c_1 FSH \cdot RcF$, indicating dependence of follicle growth on FSH. Atresia of follicles within the recruited stage is not modelled explicitly, but is assumed to be part of parameter c_1, which is considered conceptually to be *net* growth rate of functional mass. Transfer of follicles to the selected stage is denoted by the term $c_2 RcF$.

Total follicular mass in the selected stage is denoted as *SeF*. This is modelled by the equation

$$\frac{dSeF}{dt} = c_2 RcF - c_3 SeF + p_1 FSH \cdot SeF^2. \tag{5}$$

The term $c_2 RcF$ denotes follicles entering the selected stage; the term $c_3 SeF$ denotes follicles leaving the selected stage and entering the dominant stage. Growth of follicles within the selected stage is denoted by the term $p_1 FSH \cdot SeF^2$, which is again a function of FSH concentration as follicles are assumed to be still responsive to FSH. Again, atresia is assumed to be part of the net growth parameter p_1.

Finally, functional mass of the dominant follicle is denoted as *DmF* and is modelled by the equation

$$\frac{dDmF}{dt} = c_3 SeF - c_4 DmF + p_2 LH \cdot DmF^2. \tag{6}$$

Here growth of the dominant follicle is a function of concentration of LH and is represented by the term $p_2 LH \cdot DmF^2$. Atresia of the dominant follicle is denoted by the term $c_4 DmF$.

Production of the ovarian hormones, oestradiol and inhibin, is dependent on follicular size exceeding a certain threshold. Following Selgrade and Schlosser (1999), Schlosser and Selgrade (2000) and Clarke et al. (2003), we model this by considering oestradiol and inhibin production to be proportional to the linear sum of total mass of follicles in the selected and dominant stages of growth. Assuming that clearance of oestradiol is proportional to bloodstream concentration of oestradiol, the rate of change in oestradiol concentration is

$$\frac{dE_2}{dt} = e_0 + e_1 SeF + e_2 DmF - \alpha_{E_2} E_2. \tag{7}$$

It is known that the dominant follicle produces proportionally larger quantities of oestradiol than selected follicles and this condition is reflected mathematically by ensuring parameters e_1 and e_2 satisfy the relationship $e_1 < e_2$.

We model bloodstream concentration of inhibin, *Ih*, in a similar way as

$$\frac{dIh}{dt} = h_0 + h_1 SeF + h_2 DmF - \alpha_{Ih} Ih. \tag{8}$$

Finally, the corpus luteum is modelled using the variable *CL* to denote its functional mass which is capable of producing progesterone. The corpus luteum is assumed to undergo logistic growth from the day after ovulation until the start of luteolysis, which is consistent with data on progesterone concentrations in Meier et al. (2009). A review of the processes initiating the start of luteolysis is given in Flint et al. (1990) and in our model it is assumed that the release of prostaglandin-F2α by the uterus, which initiates luteolysis of the corpus luteum, occurs after the uterus has been exposed to a certain cumulative amount of progesterone. The amount of prostaglandin-F2α released during a cycle is given by the following integral:

$$Total_{P_4} = \int_{t_i}^{t_i + t_p} P_4 dt.$$

Here the value t_i denotes the time at which an oestrous cycle starts and $t_i + t_p$ is the time at which prostaglandin-F2α is released, which averages approximately 16 days in normal cycles. Note that it is the value of t_p which is determined in this integration. Because t_p is not fixed, changes in either $Total_{P_4}$ or growth rate of the corpus luteum will be reflected in the value of t_p and timing of luteolysis. An equation modelling the concentration of progesterone P_4 is given later and the threshold quantity of $Total_{P_4}$ is chosen to provide a realistic time of luteolysis.

To determine the end of an oestrous cycle, and (possibly) the start of a new cycle, the point of ovulation is determined by when the concentration of LH decreases through a threshold value. This threshold value is denoted as $T_{ov,LH}$ and is chosen to be sufficiently large to respond only to LH decreasing after the LH surge prior to ovulation, but not following small increases in LH concentration at other stages of the cycle.

The equation used to model logistic growth of the corpus luteum is

$$\frac{dCL}{dt} = r_{growth} CL\left(1 - \frac{CL}{CL_{max}}\right) \quad \text{for } t_i < t \le t_i + t_p, \tag{9}$$

where *CL* denotes the functional mass of the corpus luteum. Here the corpus luteum grows during the time interval $t_i < t \le t_i + t_p$. After prostaglandin-F2α is released at time $t_i + t_p$ the corpus luteum undergoes luteolysis. During the luteolysis stage, the actual mass of the corpus luteum may not change markedly but we assume the functional mass of the corpus luteum undergoes exponential decay and is modelled as

$$\frac{dCL}{dt} = -r_{decay} CL \quad \text{for } t_i + t_p < t < t_{i+1}. \tag{10}$$

Release of progesterone into the bloodstream is assumed to be proportional to functional mass of the corpus luteum, *CL*, and progesterone clearance proportional to the concentration of progesterone in the bloodstream. This gives us the following equation for the rate of change in bloodstream concentration of progesterone P_4

$$\frac{dP_4}{dt} = c_{P_4} CL - \alpha_{P_4} P_4. \tag{11}$$

The resulting changes in progesterone concentration due to the exponential decay of the functional mass of the corpus luteum agree with the work of Meier et al. (2009).

The values and units for the parameters used to model the ovary are given in Table 2. Note that some parameters (e.g. $c_2 - c_4$) are assigned the same value across stages because insufficient experimental data are available to ascribe different values. We

believe that such parameters are likely to vary, however, so we leave them separate for future model flexibility.

3. Results and discussion

The results of the model are now presented and it is demonstrated that either two or three follicular waves can occur per oestrous cycle. Furthermore the model is tested under different scenarios including nutritional effects and pharmacological intervention.

Predicted hormone concentrations over two oestrous cycles, each approximately 22 days long, are plotted in Fig. 2. Concentrations of GnRH and luteinizing hormone increase sharply prior to ovulation on days 22 and 44 and this occurs in the model due to a decrease in the concentration of progesterone. It can be seen from the concentrations of FSH and oestradiol that three waves of follicular growth occur per oestrous cycle, with waves of increasing oestradiol concentration corresponding to follicular growth. We note that the main features of variations in hormone concentration are modelled. For example the surge in GnRH occurs when the concentration of progesterone is sufficiently low and oestradiol increases after a rise in FSH due to increased follicular growth. Predicted progesterone concentration follows the characteristic profile of a bovine oestrous cycle with concentration decaying from day 16 (approximately) until ovulation on day 22. Overall, predicted hormone concentrations shown in Fig. 2 agree with expectations from known biology both qualitatively, in terms of relationships between hormones and their profiles, and quantitatively, in that hormone concentrations are of a similar order of magnitude compared to our experimental data (Webb et al., 1980; Gong et al., 2002).

To illustrate the flexibility of the model we now demonstrate how the model predicts inherent differences between animals, and responses to dietary or pharmacological interventions, which may affect the bovine oestrous cycle. The parameters of the model are critical to producing the correct outcomes and varying their values can have significant effects on predicted hormone concentrations. It is important, therefore, that predicted outcomes are tested against known biology.

3.1. Variance between cows

The number of follicular waves per oestrous cycle is typically either two or three; two-wave cycles are shorter (19–20 days) than three-wave cycles (21–22 days) (Adams et al., 2008). The number of waves tends to be consistent within cows (Burns et al., 2005; Adams et al., 2008), so it was necessary to ensure that the model accounted for this fundamental variation. In Fig. 3 the hormone concentration profiles for a two wave cycle are plotted and this solution was obtained by varying the parameters controlling follicular growth and time of luteolysis (through the parameter $Total_{P_4}$). We note that the time taken to complete our

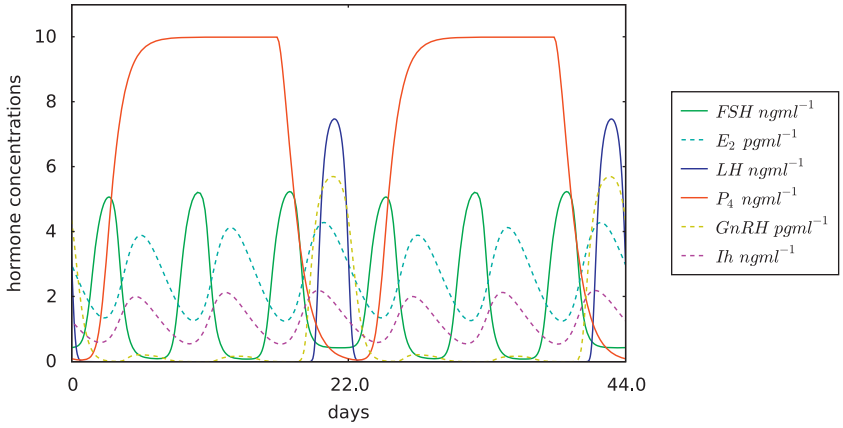

Fig. 2. Predicted concentrations for luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone (P_4), oestradiol (E_2), inhibin (Ih) and gonadotrophin-releasing hormone (GnRH) over two oestrous cycles, each exhibiting three follicular waves. The parameters used by the model are in Tables 1 and 2.

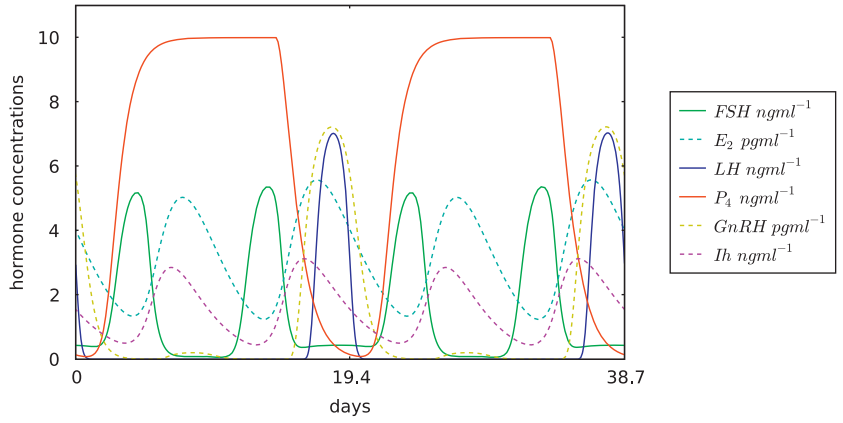

Fig. 3. Two-wave oestrus cycles showing predicted profiles for luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone (P_4), oestradiol (E_2), inhibin (Ih) and gonadotrophin-releasing hormone ($GnRH$). The length of each oestrous cycle is 19 days. The parameters are the same as in Tables 1 and 2 except that the following parameters are altered: $\alpha_{GnRH}=1.648$, $a=0.0066$, $c_1=0.035$, $c_2=0.63$, $c_3=0.63$, $c_4=0.67$, $p_1=p_2=0.15$, $e_0=0.0067$, $e_1=1.5$, $e_2=7.5$, $\alpha_{E_2}=0.75$ and $Total_{P_4}=110$.

two-wave cycle is 19 days, which is consistent with observations (Kulick et al., 2001).

Producing a model which predicts either two or three wave cycles by varying a few parameters gives confidence that the main features of the bovine oestrous cycle have been modelled correctly and that the model can include variances between individual cows. The parameters that were varied are those that affect: growth rates of selected and dominant follicles, which are slower in two-wave cycles; emergence of the second follicular wave, which is one day later in two-wave cycles; and regression of the corpus luteum, which is three days earlier in two-wave cycles. These parameters are known to be variable among cows, but relatively consistent within cows (Burns et al., 2005; Adams et al., 2008). The causes and reasons for this variation are uncertain. What is certain is that wave pattern tends to be repeatable within individuals, and duration of dominance of the first wave is predictive of the wave pattern (Adams et al., 2008).

3.2. Nutritional effects of the model

We now study how varying certain model parameters, which are likely to be influenced by diet and nutrition, affects model outputs. The model predictions which we consider are the mass of the dominant follicle at ovulation and the length of an oestrous cycle. As discussed, many other factors affect fertility, including how many follicles are recruited, size of follicles at the selected stage, quality of the oocyte, and function of the corpus luteum, but these are not considered here.

Parameters of the model known to be affected by nutritional status of the animal are listed in Table 3. These parameters were chosen for investigation on the basis of evidence in the literature (see discussion above). The list is not intended to be complete, and we acknowledge that some parameters may be affected by genetics and environmental factors as well as by nutrition. Many of these parameters affect the 'functionality' of the animal; they are related to how quickly hormones are released in response to changes in concentration of other hormones, recruitment and growth rates of follicles, or how quickly hormones are cleared (by the liver) from the bloodstream.

We now give three examples of how we can both test the mathematical model and learn about features of the bovine oestrous cycle from the model. The three examples are: (i) varying parameter a, which denotes sensitivity of pre-antral follicles to FSH and therefore controls the rate at which follicles are recruited from the primordial follicles/ovarian reserve; (ii) reducing LH release, as seen in post-partum cows with negative energy balance; and (iii) a pharmacological effect where high progesterone concentrations are maintained to mimic non-regression of the corpus luteum.These examples were chosen on the basis that they are relevant to physiological phenomena observed in practice, there is reasonable agreement on the mechanisms involved, they involve a single model parameter, and we have good biological data against which to test model predictions. Although there is evidence in the literature for nutritional effects on the other parameters listed in Table 3, such effects tend to be confounded by changes in more than one parameter.

3.2.1. Example (i)—varying a, sensitivity of pre-antral follicles to FSH, by nutrition

We have observed that diets which induce high circulating concentrations of insulin stimulate follicle recruitment (Gutierrez et al., 1997; Garnsworthy et al., 2008b) and lead to earlier resumption of postpartum oestrous cycles in dairy cows (Gong et al., 2002). Parameter a is the sensitivity of pre-antral follicles to FSH and essentially controls the mass of follicles recruited from the pre-antral follicles/ovarian reserve. Recruitment of follicles requires FSH, but the number recruited, and their continued growth, depends upon expression of mRNA for gonadotrophin receptors—i.e. the sensitivity of follicles to gonadotrophins (Bao et al., 1997). This may explain, for example, why a greater number of follicles can be recruited in heifers on a high plane of nutrition without any difference in circulating FSH concentration (Gutierrez et al., 1997), and why some cows may recruit a larger number of small follicles but have lower FSH than other cows (Burns et al., 2005). Increasing a has the effect of increasing the total mass of follicles recruited, which has subsequent effects on the rest of the follicular wave. Fig. 4 shows the nonlinear effect of varying parameter a, sensitivity of pre-antral follicles to FSH, on

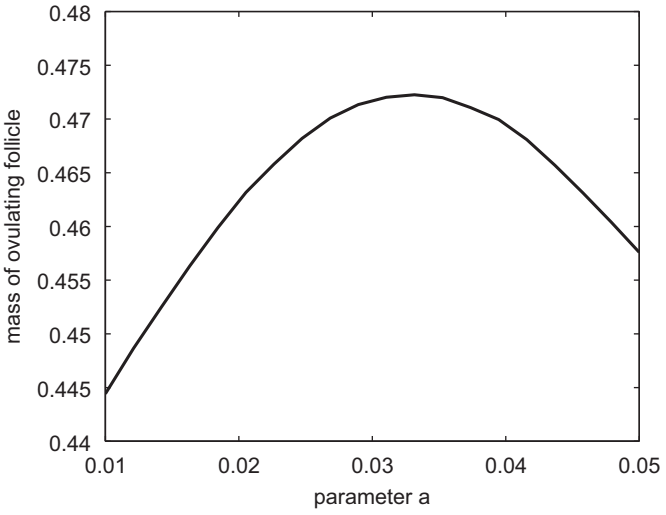

Fig. 4. Effect of varying parameter a, controlling the mass of recruited follicles, on functional mass of the ovulating follicle. Model parameters were the same as in Fig. 2 except that parameter a was varied.

Table 3
Parameters of the model known to be affected by nutritional status.

Parameter	Description	Nutritional influence	Possible signal	Ref.
k_{GnRH}	Release rate of *GnRH*	Energy balance	Neuronal	2
k_{LH}	Release rate of *LH*	Energy balance	Insulin, IGF-I	1
k_{FSH}	Release rate of *FSH*	Energy balance	Insulin, IGF-I	3
α_{LH}	Clearance rate of *LH*	Dry matter intake	Liver blood flow	[4]
α_{FSH}	Clearance rate of *FSH*	Dry matter intake	Liver blood flow	[4]
α_{E_2}	Clearance rate of E_2	Dry matter intake	Liver blood flow	4
α_{P_4}	Clearance of P_4	Dry matter intake	Liver blood flow	4
a	Follicle sensitivity to *FSH*	Energy balance	Insulin	1, 3
c_1	Follicle growth due to *FSH*	Energy balance	Insulin	1, 3
p_1	Growth of selected follicles	Energy bal, Diet fat	Insulin, NEFA	1, 3
p_2	Growth of dominant follicle	Energy bal, Diet fat	Insulin, NEFA	1, 3

Refs: 1. Butler (2003) 2. Diskin et al. (2003) 3. Webb et al. (2004) 4. Wiltbank et al. (2006) [4]=deduced from 4.

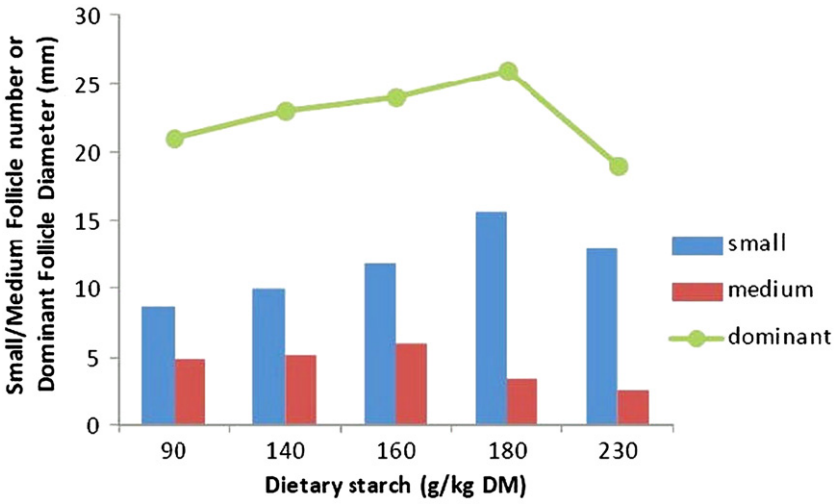

Fig. 5. Effect of five diets varying in starch content on numbers of small and medium follicles pre-ovulation, and on diameter of the ovulatory follicle in high-yielding dairy cows (Data from Garnsworthy et al., 2008b).

the mass of the dominant follicle at the point of ovulation. Increasing recruited follicles by altering parameter a is effective only up to a certain point; beyond this it has a negative effect on the mass of the ovulating follicle. This outlines an effect which the model is able to predict, but that experimentally might be unexpected. The model predicts that there is an optimum number of follicles to be recruited. If fewer follicles are recruited, then not enough oestradiol and inhibin are produced by follicles to stimulate GnRH or suppress FSH adequately at key stages of the cycle; if too many follicles are recruited, then too much oestradiol and inhibin are produced, over-suppressing FSH and inhibiting follicular growth. Recruiting either too few or too many follicles, therefore, leads to a dominant follicle with a submaximal mass, and optimising the size of the ovulating follicle may improve fertility. Recruitment of follicles is influenced by nutrition, acting through metabolic hormones such as insulin, and the response is nonlinear, as illustrated in Fig. 5 (Garnsworthy et al., 2008b). In Fig. 5, it can be seen that the numbers of small and medium-sized follicles, and the diameter of the ovulatory follicle, all showed curvilinear responses to dietary starch content (through circulating insulin). In the context of model predictions, these results suggest that medium-sized follicles are suppressed when dietary starch content is above 160 g/kg DM (>12 small follicles recruited) and that diameter of the dominant follicle is reduced when dietary starch content is above 180 g/kg DM (16 small follicles recruited). Being able to explain effects of nutrition on fertility is complicated, but we can see from this example that changes in the model parameters can provide new insights to explain nonlinear responses observed in practice. It would be unusual, if not impossible, to measure all relevant parameters in one experiment. Although the study of Garnsworthy et al. (2008b) included measurement of many production, metabolic, endocrine and ovarian responses to nutrition, sensitivity of pre-antral follicles to FSH could not be measured without disrupting the main experimental protocol. Modelling outcomes suggest that this parameter could be a useful focus of future experimentation.

3.2.2. Example (ii)—reducing rate of LH release

For the second example we vary the release rate of LH to illustrate a dynamic (i.e. time dependent) behaviour often observed during the early postpartum period. Negative energy balance during the early postpartum period is a major cause of delayed resumption of oestrous cycles (Garnsworthy et al., 2008a) and acts by suppressing pulsatile LH release (Butler, 2003).

Fig. 6 shows the effect when parameter k_{LH}, is restricted to 50% of its normal value (given in Table 1) for days 0–15 postpartum and returns linearly to its normal value between days 15 and 50. The predicted outcome is that although follicular waves are seen from day 0 onwards, normal oestrous cycles are not resumed until an LH surge is large enough to induce ovulation at day 48. This agrees with the observed effects of negative energy balance on LH release (Butler, 2003). Further modelling and biological research is needed to tease apart the factors that determine release of LH. In this simple test of the model we altered only parameter k_{LH}; in practice, clearance and GnRH-stimulation of LH are also likely to play a role in attenuated LH. The model can be used to predict theoretical responses and interactions among parameters, which can then be tested by experimentation before modelling nutritional effects on LH release.

3.2.3. Example (iii)—pharmacological elevation of progesterone

A constant high level of progesterone is often observed naturally when prostaglandin-F2α released by the uterus is insufficient to trigger luteolysis, so the corpus luteum does not regress; this syndrome is termed a persistent corpus luteum. Progesterone can also be elevated pharmacologically by administering intra-vaginal progesterone implants, a routine veterinary treatment for cows with poor corpus luteum function or for synchronising oestrous cycles in a group of animals. To simulate these scenarios, we maintained progesterone at an artificially high level after the second ovulation at day 44, whilst keeping all other model parameters constant. Predicted hormone concentrations are shown in Fig. 7.

We see that after day 44 waves of FSH, E_2 and Ih, and thus waves of follicular growth and atresia, continue. However, there is no surge in concentration of GnRH, and hence no LH surge, so ovulation does not occur. This is typically what is observed in studies of cows with a persistent corpus luteum or following progesterone administration; follicular waves continue, but the dominant follicle fails to ovulate. Kulick et al. (2001) stated that periodic follicular waves occur not only during the oestrous cycle, but also during pregnancy, the postpartum period, the prepubertal period, and prolonged progesterone administration. The model in this case agrees with observed biology, which gives us confidence in the validity of our modelling assumptions.

Although the model simulates the outcomes of elevated progesterone accurately, a greater challenge would be to explore nutritional influences on parameters that might result in progesterone elevation due to a persistent corpus luteum. Inadequate

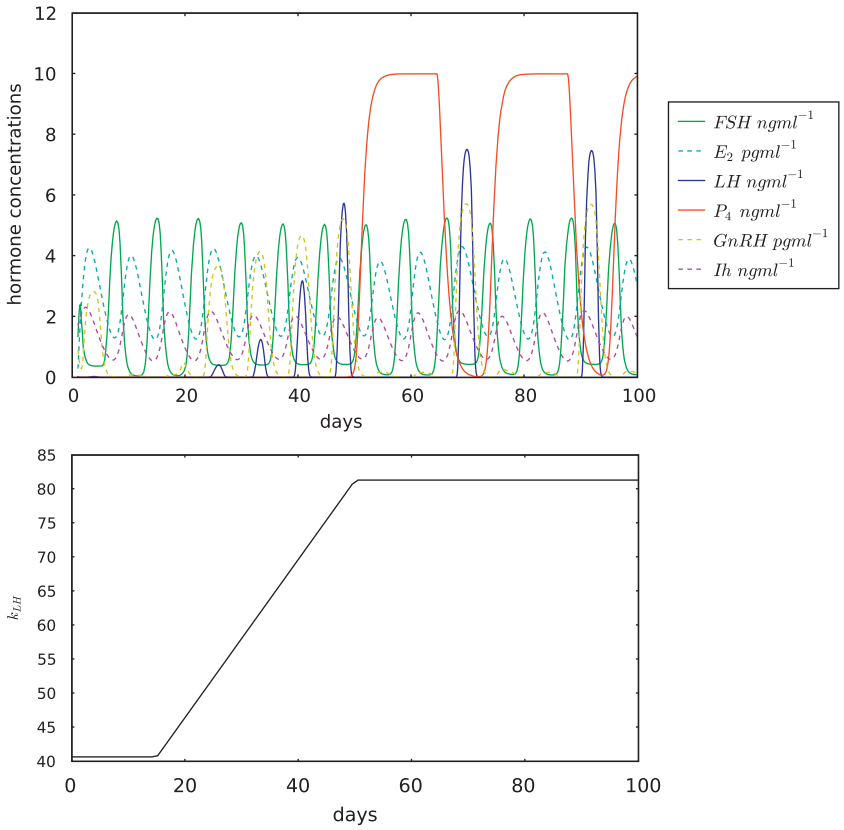

Fig. 6. Prediction of resumption of normal oestrous cycles after parturition. Here the parameter k_{LH} controlling the release of LH is attenuated over the first 50 days postpartum. Parameters are the same as in Fig. 2 except that parameter k_{LH} is varied over time as shown in the bottom panel.

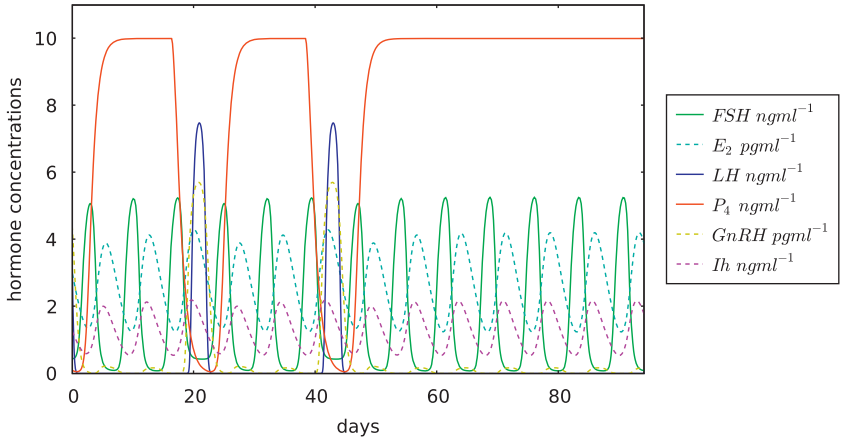

Fig. 7. Hormone concentrations predicted by the model when progesterone concentration P_4 is kept artificially high after the second ovulation from day 44 onwards; all other model parameters are as in Tables 1 and 2.

prostaglandin-F2α release is a predisposing factor for a persistent corpus luteum. The model assumes that this is determined by the threshold value for cumulative exposure to progesterone and by functional growth rate of the corpus luteum. Whether these parameters are affected by nutrition is unknown, so further research is required.

3.3. Sensitivity analysis

To indicate the sensitivity of the model to changes in parameter values, each of the parameters in Tables 1 and 2 was increased and decreased individually by 5%. An incremental range of $\pm 5\%$ was chosen as standard for all parameters because the model failed to integrate when some parameters (e.g. k_{FSH} and α_{FSH}) were changed by $\pm 10\%$. The effects on length of the oestrous cycle and mass of the dominant follicle, expressed as percentage change per one percent increase in each parameter value, are shown in Table 4.

Length of the oestrous cycle was not very sensitive to changes in individual parameter values over the range studied. In all cases, a change of 1% in a parameter value resulted in a change of less than 0.6% (approximately 3 h) in length of the oestrous cycle. Parameters eliciting the greatest response in cycle length ($>0.3\%$) were clearance rate of FSH (α_{FSH}), clearance rate of oestradiol (α_{E_2}) and rate of disappearance of selected follicles (c_3), which were all related negatively to cycle length, followed by

Table 4
Sensitivity analysis: percentage change in length of oestrous cycle (OC length) and mass of dominant follicle (DF mass) per 1% increase in each parameter value from 5% below to 5% above values in Tables 1 and 2.

Parameter	OC length	DF mass	Parameter	OC length	DF mass
k_{LH}	−0.06	0.07	a	−0.06	0.07
$n_{LH,GnRH}$	0.00	0.23	c_1	0.31	4.91
$T_{LH,GnRH}$	0.00	−2.69	c_2	−0.17	−0.68
α_{LH}	0.00	1.00	c_3	−0.32	0.50
k_{GnRH}	0.00	2.70	c_4	0.00	−2.35
n_{GnrH,P_4}	0.00	0.00	p_1	−0.01	0.08
T_{GnRH,P_4}	0.00	−0.19	p_2	0.00	1.08
n_{GnrH,E_2}	0.00	0.32	e_0	0.00	−0.01
T_{GnRH,E_2}	0.00	−1.94	e_1	−0.11	−0.86
α_{GnRH}	0.01	−2.32	Ne_2	0.15	0.00
k_{FSH}	−0.24	4.89	α_{E_2}	−0.42	−0.99
$n_{FSH,Ih}$	0.06	1.10	h_0	0.00	0.00
$T_{FSH,Ih}$	0.09	1.26	h_1	−0.07	−0.77
n_{FSH,E_2}	0.05	0.66	h_2	−0.03	−0.52
T_{FSH,E_2}	−0.04	2.77	α_{Ih}	0.04	1.00
$k_{FSH,GnRH}$	0.00	0.15	r_{growth}	0.00	0.05
$n_{FSH,GnRH}$	0.00	0.09	r_{decay}	0.00	−0.04
$T_{FSH,GnRH}$	0.00	−0.02	CL_{max}	0.01	0.43
α_{FSH}	−0.59	−7.67	c_{P_4}	0.01	0.43
$T_{ov,LH}$	0.00	0.07	α_{P_4}	−0.01	−0.33
			$Total_{P_4}$	−0.02	−0.32

growth rate of follicles due to *FSH* (c_1), which was related positively to cycle length. The general lack of sensitivity for cycle length is perhaps related to the consistency of follicular waves and length of the oestrous cycle within cows (Burns et al., 2005; Adams et al., 2008). It also explains why some parameters had to be varied by between 10 and 90% when we compared three-wave cycles (Fig. 2) and two-wave cycles (Fig. 3).

Mass of the dominant follicle was sensitive to changes in a number of parameter values. Parameters eliciting the greatest response ($>1\%$) can be grouped into: parameters associated with FSH, i.e. FSH clearance rate (α_{FSH}), FSH release rate (k_{FSH}), growth rate of follicles due to *FSH* (c_1), thresholds for negative feedback of E_2 and *Ih* on *FSH* (T_{FSH,E_2} and $T_{FSH,Ih}$) and exponent for positive effect of *GnRH* on *FSH* ($n_{FSH,Ih}$); parameters associated with GnRH, i.e. GnRH release rate (k_{GnRH}), GnRH clearance rate (α_{GnRH}), threshold for positive effect of *GnRH* on *LH* ($T_{LH,GnRH}$) and threshold for positive feedback of E_2 on *GnRH* (n_{GnrH,E_2}); and parameters associated with dominant follicle growth (p_2) and atresia (c_4). It is not surprising that FSH has a major influence on mass of the dominant follicle because both mathematically (Eqs. (4) and (5)) and physiologically (Webb et al., 2007) FSH controls rate of follicular growth to the selected stage. Follicle mass at the selected stage in turn determines mass of the dominant follicle both directly (Eq. (6)) and indirectly through feedback of oestradiol and inhibin. GnRH parameters showed lower sensitivity than FSH parameters but, nevertheless, play important roles in follicular growth through control of FSH and LH release (Eqs. (1) and (3)).

Many of these parameters cannot be quantified easily in vivo, so verification of sensitivity is difficult at the individual parameter level. Furthermore, it is likely that some parameters might not vary independently, and that interactions exist between some parameter values, but this sensitivity analysis suggests some areas for future research effort. Both cycle length and mass of the dominant follicle are important factors in overall reproductive efficiency and have been linked to nutrition (Lucy et al., 1991; Boland et al., 2001; Butler, 2003; Wiltbank et al., 2006; Webb et al., 2007).

3.4. Model limitations and future refinements

Our aim in this work was to build a model that would capture the main features of the oestrous cycle, allowing us to investigate mathematically the effects of diet and pharmacological interventions on the dynamics of the system. In accordance with the ethos of Vetharaniam et al. (2010), we deliberately simplified details of underlying mechanisms in order to minimise the number of parameters and optimise practicality in this initial model. The resulting framework leaves scope, however, for refinement and extension where these might improve the predictive ability or utility of the model.

The way in which the corpus luteum has been modelled could be improved with additional hormones and growth factors which regulate the growth/regression of the corpus luteum. However, biological understanding of the exact mechanism by which the corpus luteum undergoes luteolysis is somewhat limited, although many factors are known to be involved (Miyamoto et al., 2009). Similarly, incorporation of a uterine sub-model might improve our ability to predict prostaglandin-F2α release either to induce luteolysis or to permit embryo implantation (Robinson et al., 2008).

From our reviews of local and systemic regulation of ovarian function (Webb et al., 2004, 2007), we know that there are many intra-ovarian factors, such as insulin-like growth factors and bone morphogenetic proteins, which provide local regulation of follicular growth and also interact with nutrition through systemic (extra-ovarian) factors. Dynamic study of these local factors in vivo is virtually impossible in the lactating dairy cow, but incorporation of these interactions into the current model would provide new insights and guide research by linking cellular scale observations to whole animal responses.

The quality of the follicle, and in particular the oocyte contained within the follicle, is paramount to the ability of the cow to become pregnant. Our current model predicts when ovulation will occur, but provides no information on the quality of the oocyte released at that ovulation. We have demonstrated in several studies that nutrition of the dairy cow can affect the developmental competence of oocytes (Fouladi-Nashta et al., 2005, 2007, 2009). It would be desirable to extend the scope of the model by including nutritional effects on oocyte quality, although the exact nature of the endocrine regulation is unclear. Vetharaniam et al. (2010) concluded that modelling in the area of oocyte quality is sparse and limited to a few models of oxygen supply to the oocyte.

We investigated behaviour of the current model by altering some parameters which we know are linked to nutrition. An area for further development is to formalise these links by incorporating mathematical models of metabolic homeostasis (Smith et al., 2009) and nutrient utilisation (Kebreab et al., 2009).

4. Conclusions

In this paper we have presented a mechanistic model which captures many of the characteristics and main features of the bovine oestrous cycle. The model incorporates feedback mechanisms of the hypothalamus–pituitary–ovarian axis and the dynamics of the ovaries including the various stages of follicular growth and the corpus luteum. The model was tested successfully by reproducing cycles with two and three follicular waves, demonstrating examples of changes in nutrition that affect follicle recruitment and ovulation, and responses to pharmacological intervention. We have shown that changes to model parameters can predict altered ovarian function that has direct and indirect effects on fertility of the animal. Although predictions of cycle characteristics agree with observations, further work is required to verify model parameters with biological data to confirm the underlying mechanisms and to validate the ability of the model to simulate atypical ovarian hormones such as prolonged luteal

phases or interruptions of cyclicity. This would also indicate how parameters could be optimised to increase fertility. It is concluded that this model provides a sound basis for exploring factors that influence the bovine oestrous cycle in order to test hypotheses about nutritional and hormonal influences which, with further validation, should help to design dietary or pharmacological strategies for improving reproductive performance in cattle.

Acknowledgments

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